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Health Effects Assessment for Cresols

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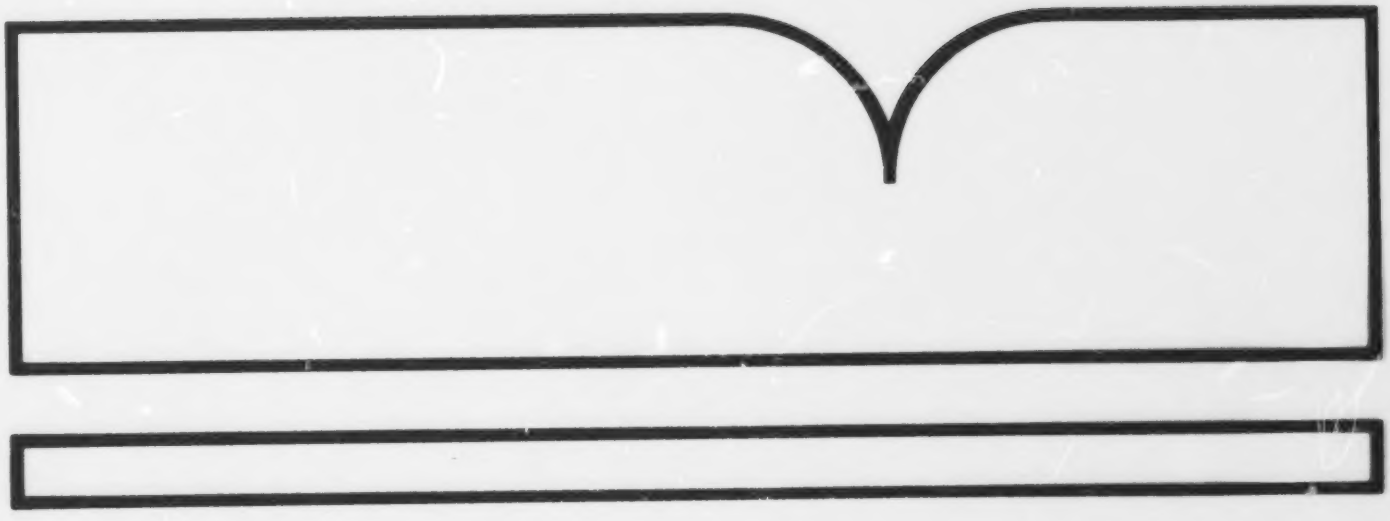

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HEALTH EFFECTS ASSESSMENT FOR CRESOLS

U.S. Environmental Protection Agency
Office of Research and Development
Office of Health and Environmental Assessment
Environmental Criteria and Assessment Office
Cincinnati, OH 45268

U.S. Environmental Protection Agency
Office of Emergency and Remedial Response
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16. ABSTRACT

This document represents a brief, quantitatively oriented scientific summary of health effects data. It was developed by the Environmental Criteria and Assessment Office to assist the Office of Emergency and Remedial Response in establishing chemical-specific health-related goals of remedial actions. If applicable, chemical-specific subchronic and chronic toxicity interim acceptable intakes are determined for systemic toxicants, or q_1^* values are determined for carcinogens for both oral and inhalation routes.

A chronic interim acceptable intake was determined for cresols based on inhalation exposure.

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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with cresols. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1982. Cresols: Hazard Assessment. Environmental Criteria and Assessment Office, Cincinnati, OH. Internal draft.

U.S. EPA. 1983b. Reportable Quantity Document for Cresol. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983a).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, q_1^*s have been computed based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment in proper context, the reader is referred to the preface of this document. The preface outlines limitations applicable to all documents in this series as well as the appropriate interpretation and use of quantitative estimates.

Oral toxicity data for cresols were not located. Therefore, an oral AIC could not be estimated. Inhalation exposure data were severely limited, but an inhalation AIC of 7.14 mg/day was estimated based on the TLV. This estimate should be reviewed as additional data become available. A CS for cresols of 21.2 based on data for bone marrow depression in rats exposed via inhalation was calculated.

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
BCF	Bioconcentration factor
CAS	Chemical Abstract Service
CNS	Central nervous system
CS	Composite score
EKG	Electrocardiogram
GI	Gastrointestinal
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

The relevant physical and chemical properties of o-cresol (CAS No. 95-48-7), m-cresol (CAS No. 108-39-4) and p-cresol (CAS No. 106-44-5), and the half-lives for the nonisomer specific cresols are given in Table 1-1.

The half-life of cresols in aquatic media has been estimated from the estimated half-life of 2 days for chlorocresols in river water (Zoeteman et al., 1980). Since the half-life of the nonchlorinated cresols is expected to be shorter than the chlorinated cresols (Mabey et al., 1981), the half-life for cresols has been estimated to be <2 days in river water.

An estimate for the half-life of cresols in soil could not be located in the available literature. Biodegradation is likely to be the most significant fate determining process for these chemicals in soils (Medvedev and Darydov, 1972). Based on the physical and chemical parameters of cresols (see Table 1-1), it is possible that these compounds may leach from soil to groundwater, particularly from soils with low organic carbon content.

TABLE 1-1

Selected Physical and Chemical Properties and Half-Lives for Cresols

Property	o-Cresol	m-Cresol	p-Cresol	Reference
Chemical class:	methylated phenol	methylated phenol	methylated phenol	NA
Molecular weight:	108.13	108.13	108.13	Verschueren, 1983
pK_a:	10.2	10.01	10.17	Weast, 1980
Vapor pressure, mm Hg at 25°C:	0.25	0.15	0.11	NIOSH, 1978
Water solubility:	31,000 mg/ℓ at 40°C	23,500 mg/ℓ at 20°C	24,000 mg/ℓ at 40°C	Verchueren, 1983
pK_{ow}:	1.95	1.95	1.95	SRI, 1978
BCF:	9	9	9	Veith et al., 1979
Half-lives of nonisomer specific cresols in:				
Air:	~3.3 hours			Cupitt, 1980
Water:	<2 days (estimated)			NA

NA = Not applicable

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

Although specific oral absorption data for o-, m- and p-cresol were not available, the likelihood that the cresols are absorbed from the GI tract can be inferred from acute oral toxicity data (Deichmann and Keplinger, 1981).

2.2. INHALATION

Although specific pulmonary absorption data for o-, m- and p-cresol were not available, the likelihood that the cresols are absorbed from the lungs can be inferred from inhalation toxicity data (Deichmann and Keplinger, 1981).

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Pertinent data regarding the subchronic oral toxicity of o-, m- and p-cresol to humans and experimental animals could not be located in the available literature.

3.1.2. Inhalation. The subchronic inhalation studies with o-, m- and p-cresol have been summarized by U.S. EPA (1982). The discussion of these studies is taken, in part, from that document.

Uzhdavini et al. (1972) exposed rats and guinea pigs to o-cresol by inhalation at a level of 9 mg/m^3, 6 hours/day, 5 days/week, for 2 months, and subsequently for 4 hours/day, 5 days/week, for 2 months. During the exposure period, the mean concentration was 9.0$\pm$0.9 mg/m^3. In the experiment with the rats, the following parameters were measured or observed: elementary conditioned defensive reflex, leukocyte levels in the peripneral blood, leukoid and erythroid elements in the bone marrow, and liver function (measured indirectly by hexobarbital narcosis). In the experiments with guinea pigs, blood counts and electrocardiograms were performed. All the exposed rats had lost the defensive reflex by the end of the second month. This parameter was also depressed in control rats, but at a slower rate. The exposed male rats had a greater number of white blood cells in the peripheral blood (~22,000/mm^3) than did the controls (~14,000/mm^3), especially by the fourth month of exposure. One month after cessation of exposure to cresol, the leukocyte count in the exposed rats had returned to essentially control values. In the female rats, no effects on leukocyte count were described. Bone marrow examination revealed that rats in the experimental groups had a statistically significant decrease in the numbers of elements in the erythroid series compared to controls, which was

reflected in a statistically significant difference in the leukoid-to-erythroid ratio (1.3:1 in exposed rats and 2.1:1 in controls). The authors suggested that cresol had an effect on the liver since the duration of hexobarbital narcosis was significantly greater in exposed rats than in controls, 62.0±5.2 minutes versus 37.4±0.7 minutes. In exposed rats there was a slight decrease in the reactivity of the pituitary-adrenal system, but it was not stated how this was measured.

In guinea pigs, inhalation exposure to o-cresol had no effect on the leukoid-to-erythroid ratio in the bone marrow. There were some unspecified changes in the hemoglobin concentration. The wave component of the QRS complex of the electrocardiogram was slightly decreased in exposed guinea pigs, but it was not indicated when these measurements were taken. Though the results from this study are difficult to evaluate because the data presented are incomplete and lacking in such information as description of exposure conditions, numbers of animals used, and control conditions, NIOSH (1978) believes that the adverse effects found by Uzhdavini et al. (1972) are meaningful since they are in general agreement with those reported by Deichmann and Witherup (1944) for acute toxicity experiments.

Kurlyandskiy et al. (1975) exposed rats to a mixture of o-, m- and p-cresol by inhalation at a level of 0, 0.0052 or 0.05 mg/m³ for 90 days (exposure interval). No treatment-related effects were seen at the 0.0052 mg/m³ level; however, at the higher dose level, treatment-related effects included CNS excitation, denaturation of lung protein and decreased body weight gain. Further details regarding the experimental protocol and effects were not available in the summaries of this Russian study.

3.2. CHRONIC

3.2.1. Oral. Pertinent data regarding the chronic oral toxicity of o-, m- and p-cresol were not located in the available literature.

3.2.2. Inhalation. Pertinent data regarding the chronic inhalation toxicity of o-, m- and p-cresol could not be located in the available literature.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Several human case studies have reported the use of Lysol®, a cresol-containing solution, as an abortifacient (Vance, 1945; Presley and Brown, 1956). In addition to abortion, intravaginal application of Lysol® produces extensive hemolysis, erosion of blood vessels, kidney tubular damage, liver necrosis and death (Vance, 1945; Presley and Brown, 1956).

Pertinent data regarding the teratogenicity of o-, m- and p-cresol in experimental animals following oral exposure could not be located in the available literature.

3.3.2. Inhalation. Pertinent data regarding the teratogenicity of o-, m- and p-cresol following inhalation exposure could not be located in the available literature.

3.4. TOXICANT INTERACTIONS

All three cresol isomers were individually tested for tumor-promoting activity on mouse skin (Boutwell and Bosch, 1959). The skin of female mice was initiated with dimethylbenzanthracene followed by the application of two drops of a 20% solution of the test cresol 6 times/week for 12 weeks. The incidence of papillomas was 59, 50 and 35% for the o-, m- and p-cresol isomers, respectively. Using the same procedure, a 5.7% solution of the m- and p-cresol isomers was tested in a 20-week study (Boutwell and Bosch,

1959). The incidences of papillomas were 24 and 29% for the m- and p-isomers, respectively. None of the mice in this study developed skin carcinomas. The tumor incidence in an initiated only control group was not presented in the reviews of this study (Battelle, 1981; U.S. EPA, 1982). Also, Kaiser (1967) and Bock et al. (1971) demonstrated promoting activity in tea and cigarette smoke condensate, both of which contain cresols.

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. Pertinent data regarding the carcinogenic effects in humans of oral exposure to o-, m- and p-cresol could not be located in the available literature.

4.1.2. Inhalation. Pertinent data regarding the carcinogenic effects in humans of inhalation exposure to o-, m- and p-cresol could not be located in the available literature.

4.2. BIOASSAYS

4.2.1. Oral. Pertinent data regarding the carcinogenic effects in experimental animals from oral exposure to o-, m- and p-cresol could not be located in the available literature.

4.2.2. Inhalation. Pertinent data regarding the carcinogenic effects in experimental animals from inhalation exposure to o-, m- and p-cresol could not be located in the available literature.

4.3. OTHER RELEVANT DATA

Pertinent data regarding the mutagenicity of o-, m- and p-cresol could not be located in the available literature.

4.4. WEIGHT OF EVIDENCE

Applying the criteria proposed by the Carcinogen Assessment Group of the U.S. EPA (Federal Register, 1984) for evaluating weight of evidence for the carcinogenicity of the cresols, data were not available regarding the carcinogenicity of the cresols in either humans or animals. The cresols are, therefore, most appropriately classified as Group D (Not classified) chemicals.

5. REGULATORY STANDARDS AND CRITERIA

Based somewhat on the subchronic inhalation studies of Kurlyandskiy et al. (1975) and Uzhdavini et al. (1972), NIOSH (1978) has recommended a TLV-TWA of 10 mg/m³ for all isomers of cresol. ACGIH (1983) recommended a TLV-TWA of 22 mg/m³ (5 ppm) for all isomers of cresol, based on analogy to phenol. The Occupational Safety and Health Administration has set a standard of 22 mg/m³ (5 ppm) for all isomers of cresol (Code of Federal Regulations, 1981).

6. RISK ASSESSMENT

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

6.1.1. Oral. The lack of pertinent subchronic oral toxicity data precludes the derivation of an AIS for subchronic exposure to o-, m- and p-cresol.

6.1.2. Inhalation. At an exposure level of 9 mg o-cresol/m^3, 6 hours/day, 5 days/week for 2 months and then for 4 hours/day, 5 days/week for 2 subsequent months, exposed guinea pigs had unspecified changes in EKGs and exposed rats had CNS effects and blood changes (Uzhdavini et al., 1972). Rats exposed to a mixture of the three cresol isomers at a level of 0.05 mg/m^3 for 90 days (exposure interval) had CNS excitation, lung protein denaturation and decreased body weight gain (Kurlyandskiy et al., 1975). The effects seen in these two Russian studies may represent a LOAEL; however, without any details regarding the severity or type of these changes, it is impossible to assert that a LOAEL was obtained. Therefore, it would be imprudent to use either of these studies to derive a value for an AIS without further information.

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

6.2.1. Oral. The lack of pertinent chronic oral toxicity data precludes the derivation of an AIC for chronic exposure to o-, m- and p-cresol.

6.2.2. Inhalation. Chronic inhalation toxicity data could not be located in the available literature. For reasons discussed in Section 6.1.2., the subchronic inhalation data from the Russian studies of Uzhdavini et al. (1972) and Kurlyandskiy et al. (1975) cannot be used to derive an AIC for chronic inhalation exposure to cresols.

U.S. EPA (1982) derived a chronic inhalation interim ADI from the TLV for cresols, and the same approach will be followed here. NIOSH (1978) evaluated the toxicity of cresols to determine a TLV to protect the health of workers. The experiments of Uzhdavini et al. (1972) and Kurlyandskiy et al. (1975) were considered inadequate as a result of the incomplete presentation of experimental design and the confusing presentation of results. It was noted, however, that the effects reported were not inconsistent with effects observed following acute exposure. Since the exposure levels reported by Uzhdavini et al. (1972) and Kurlyandskiy et al. (1975) were lower than the TLV of 22 mg/m³ (5 ppm) recommended by ACGIH (1979, 1983), and the ACGIH (1979, 1983) TLV was based primarily by analogy to the toxic effects of phenol, NIOSH (1978) recommended a TLV of 10 mg/m³. Because of the limited information on the chronic inhalation toxicity of cresols, NIOSH (1978) did not totally disregard the studies of Uzhdavini et al. (1972) and Kurlyandskiy et al. (1975), but did not give them the weight of an adequately performed toxicity study.

Using the TLV of 10 mg/m³ recommended by NIOSH (1978) for cresols (singly or as a mixture), a chronic inhalation interim AIC for humans can be derived. The TLV of 10 mg/m³ is adjusted to units of mg/kg/day by multiplying by an assumed human breathing volume of 10 m³/day and 5/7 to convert from a 5-day work week to continuous exposure. This gives a dose of 71.43 mg/day. An uncertainty factor of 10 is applied to protect the more sensitive individuals of a population. This gives a chronic inhalation AIC of 7.143 mg/day.

Cresol has been subjected to RQ ranking based on chronic toxicity. Only one CS was calculated and it was based on the effect of depression of erythropoeisis in the bone marrow of male rats exposed to o-cresol vapor at 9.0

mg/m³, 6 hours/day, 5 days/week for 2 months and then for 4 hours/day, 5 days/week for an additional 2 months. A human MED was calculated by expanding to continuous exposure, assuming a human inhalation rate of 20 m³/day and an absorption factor of 0.5, and by applying an uncertainty factor of 10 to extrapolate from subchronic to chronic exposure. The human MED of 1.34 mg/day corresponds to an RV_d of 5.31. An RV_e of 4 was chosen to represent the effect of bone marrow depression. A CS of 21.2, the product of RV_d and RV_e, resulted. This is in agreement with U.S. EPA (1983b).

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. The lack of carcinogenicity data precludes the derivation of a carcinogenic potency for oral exposure to cresols.

6.3.2. Inhalation. The lack of carcinogenicity data precludes the derivation of a carcinogenic potency for inhalation exposure to cresols.

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APPENDIX

Summary Table for o-, m- and p-Cresol

	Species	Experimental Dose/Exposure	Effect	Acceptable Intake (AIS or AIC)	Reference
Inhalation					
AIS					
AIC	humans	10 mg/m³	TLV	7.14 mg/day	NIOSH, 1978
Maximum composite score	rats	9.0 mg/m³ 5 hours/day, 5 days/week for 4 months (RV_d=5.3)	bone marrow depression (RV_e=4)	21.2	Uzhdavini et al., 1972
Oral					
AIS				NA	
AIC				NA	

NA = Not available